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# Effects of Repository Corticotropin Injection on Medication Use in Patients With Rheumatologic Conditions: A Claims Data Study

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**Abstract**

**Background:** Currently, specific studies identifying how repository corticotropin injection (RCI) is used in rheumatologic conditions are lacking. This is a first step to familiarize the trends of demographics using RCI as well as other medication use. **Objective:** RCI may produce anti-inflammatory as well as immune-modulatory effects. The purpose of this study is to examine the demographics of those who use RCI and the change in medication use, specifically prednisone, after RCI initiation. **Method:** This study used the Symphony Health Solutions (SHA) Claims database from 2008 to 2015. International Classification of Disease, Ninth Revision, codes were used to identify rheumatologic conditions including rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, and polymyositis. Information including RCI dose and concomitant medication uses was also obtained. **Results:** A total of 2749 patients with rheumatologic conditions receiving RCI were investigated for demographic information, and a total of 1048 patients with rheumatologic conditions on RCI were examined for medication use. The use of nonsteroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs, and biologics overall decreased significantly in all 3 rheumatologic conditions except biologics in dermatomyositis/polymyositis. In addition, mean prednisone dose before and after RCI use significantly decreased one quarter (12 weeks) after RCI initiation. **Conclusion:** Claims-based study on RCI use indicates that RCI use might reduce use of prednisone, disease-modifying anti-rheumatic drugs, and other biologics. Further prospective study is needed.

**Keywords**

rheumatoid arthritis, systemic lupus erythematosus, corticosteroids, databases, nonsteroidal anti-inflammatory drugs

## Introduction

Repository corticotropin injection (RCI; H.P. Acthar Gel) is a gel preparation of adrenocorticotropic hormone ($ACTH_{1-39}$) derived from porcine pituitary and formulated into a repository gel for prolonged release.[1] One of the actions of ACTH stimulates the adrenal cortex to secrete cortisol, corticosterone, and aldosterone.[2] Previously, the effect of RCI was thought to be through stimulation of endogenous cortisol production in the adrenal gland. More recently, it has been shown that RCI binds to and activates all 5 known melanocortin receptors (MC1R to MC5R).[3] Thus, RCI may produce anti-inflammatory and immunomodulatory effects by directly activating MCRs.[1]

RCI was originally approved by the US Food and Drug Administration in 1952.[2] The Food and Drug Administration–approved indications include infantile spasms, multiple sclerosis, rheumatologic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, respiratory diseases, and edematous states.[2] Approved rheumatologic indications include rheumatoid arthritis (including juvenile rheumatoid arthritis), systemic lupus erythematosus, systemic dermatomyositis, polymyositis, psoriatic arthritis, and ankylosing spondylitis.[2]

The purpose of this study is to analyze prescription patterns of RCI in patients with rheumatologic conditions and to examine the trend of other prescription medication use, especially prednisone, after RCI administration.

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**Table 1.** Demographic Characteristics of Patients With RA, SLE, DM/PM on RCI.

| Analysis Category | RA | SLE | DM/PM |
|---|---|---|---|
| Age (average in years) | 59.1 | 48.1 | 55.5 |
| Number of patients on RCI, n (%) | 1269 (46.2) | 874 (31.8) | 606 (22.0) |
| Gender, % female | 78 | 89 | 70 |
| RCI dose administered | | | |
| 80 Units, 2×/week (%) | 58 | 57 | 68 |
| 200 Units/week (%) | 12 | 15 | 16 |
| Average RCI duration, days | 115.7 | 129.2 | 157.1 |

Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; DM, dermatomyositis; PM, polymyositis.

## Method

### *Study Design and Data Source*

This study used data from an administrative health care claims database, the Symphony Health Solutions (SHA) Claims database (2008-2015). SHA Claims data is a database that captures health events in 17 out of every 20 people in the United States. These claims are obtained in each of the US states and include all insurance types, including Medicare and Medicaid.[4] Each patient in the database has a unique encrypted identifier assigned by Symphony. The data are de-identified and fully compliant with all Health Insurance Portability and Accountability Act (HIPAA) privacy and security requirements to protect participant anonymity and confidentiality. No direct interaction with patients was involved in this study, and an institutional review board review was not required for this study.

Both pediatric and adult patients newly initiated on RCI for rheumatologic conditions were included in the analysis. Diagnoses were recoded using the International Classification of Disease, Ninth Revision (ICD-9). Rheumatologic conditions included rheumatoid arthritis (RA; ICD-9 codes 714.0, 714.30, 714.31, 714.32, 714.33), systemic lupus erythematosus (SLE; ICD-9 code 710.0), dermatomyositis (DM; ICD-9 code 710.3), and polymyositis (PM; ICD-9 code 710.4).

To minimize uncertainty of diagnosis, patients were included only if they had claims for the same rheumatologic ICD-9 diagnosis code at least twice. Patients with multiple sclerosis (ICD-9 code 340), proteinuria (ICD-9 code 791.0), and other nephrotic disorders or nephritis (ICD-9 codes 581, 582, and 583) unrelated to rheumatologic conditions were excluded; patients with a diagnosis of nephritis and proteinuria ICD-9 code more than zero time and rheumatologic diagnoses less than 2 times were excluded. Available information included (1) demographic information (age and gender), (2) RCI dose, (3) duration of RCI use, (4) concomitant medication during/before/after RCI use, and (5) mean prednisone dose before and after RCI initiation. Claims information for steroids and disease-modifying antirheumatic drugs (DMARDs) other than biologics/steroids were obtained though outpatient (CMS 1400), institutional (CMS 1500), and pharmacy claims. Each claim had data on the prescriber, date, units, and days of supply.

Patients were followed longitudinally, and only patients with claims 2 years prior to first RCI use and 1 year after the last RCI use were included. Comparisons were made to evaluate steroid, biologic, nonsteroidal anti-inflammatory drug (NSAID), and conventional DMARD (methotrexate, leflunomide, tacrolimus, mycophenolate, azathioprine, sulfasalazine, cyclophosphamide, hydroxychloroquine, and cyclosporine) use 6 months before, during, and 6 months after RCI use. The mean prednisone dose for those who received prednisone in the 2 consecutive quarters (24 weeks) was compared before and after RCI use.

Paired 2-tailed *t* test was used to calculate the *P* values for each class of drug before/after RCI scenarios.

## Results

Out of 2.7 million rheumatologic patients in the Symphony SHA Claims database over a 6-year period, there were a total of 2749 patients who used RCI, including 1269 RA patients, 874 SLE patients, and 606 with DM/PM (Table 1). The mean age for each group was 59.1 years (RA), 48.1 years (SLE), and 55.5 years (DM/PM). The majority of RCI users were female, and the most commonly used dose was 80 units, twice a week, administered intramuscularly or subcutaneously (Table 1).

There were 504 RA patients, 322 SLE patients, and 222 DM/PM patients evaluated for biologics, NSAIDs, and conventional DMARDs after RCI use. Medication use was analyzed 6 months before and 6 months after RCI use. On average, patients were on RCI 116 days for RA, 129 days for SLE, and 157 days for DM/PM. Prednisone use decreased from 67% of patients to 54% for RA, 73% to 58% for SLE, and 76% to 58% for DM/PM. The decline in percentage of patients who used prednisone was significant for all 3 disease entities as indicated by *P* value <.05 (Figure 1a-c).

In addition to prednisone use, the use of NSAIDs, DMARDs, and biologics overall decreased significantly in all 3 rheumatologic conditions except for the use of

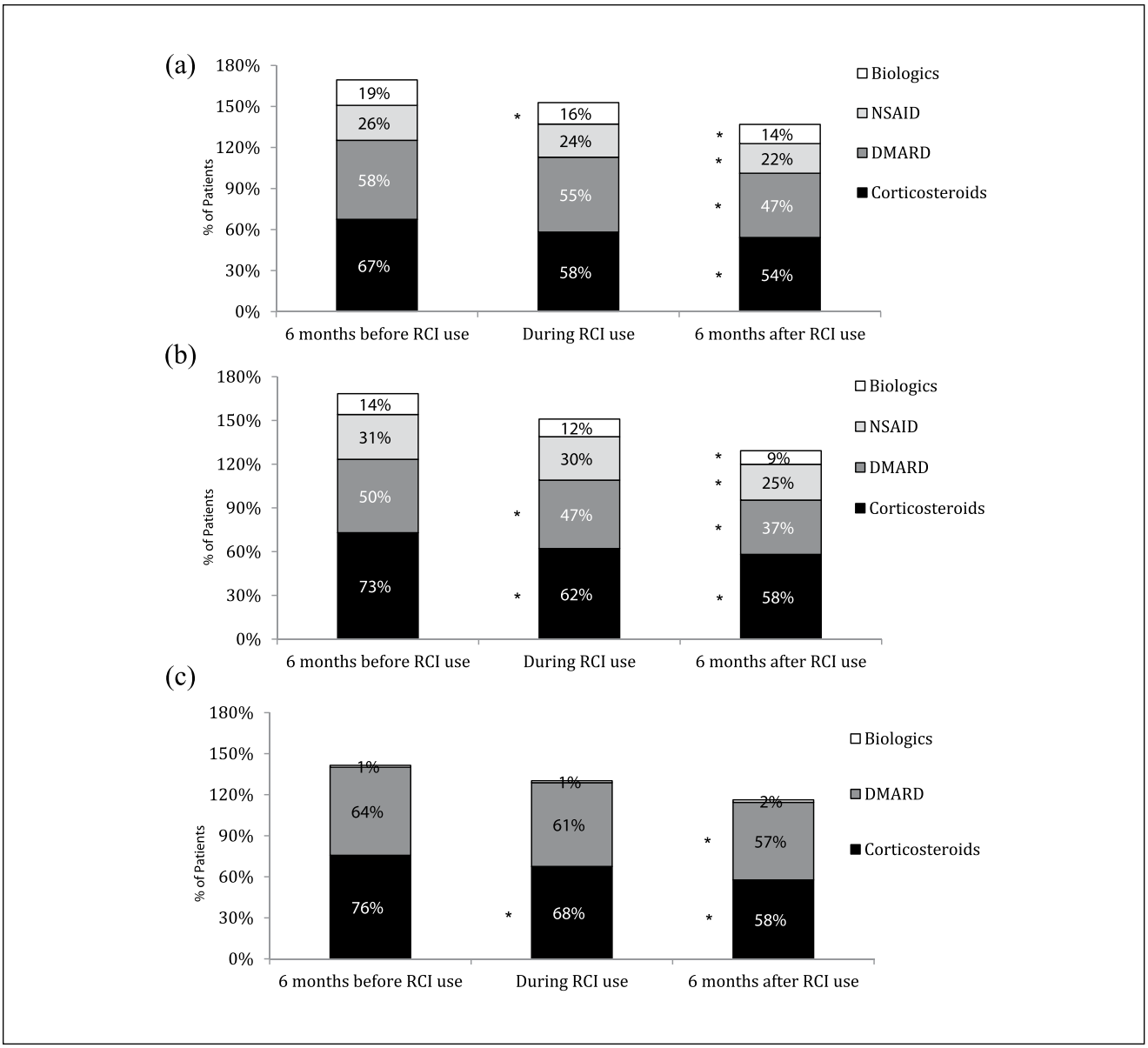


**Figure 1.** (a) Change in medication use before, during, and after RCI use in RA. There was a significant decrease in the percentage of patients on biologics, NSAIDs, DMARDs (other than biologics), and corticosteroids at 6 months after RCI use compared to initial 6 months before RCI use. Included were patients who were on corticosteroids at any point over the period of 12 months. *Indicates $P < .05$ (comparison between 6 months after RCI use and 6 months before RCI use). (b) Change in medication use before, during, and after RCI use in SLE. *Indicates $P < .05$. (c) Change in medication use before, during, and after RCI use in DM/PM. *Indicates $P < .05$.

biologics in DM/PM (NSAIDs use not available in DM/PM; Figure 1a-c).

Further analysis was done to examine the mean prednisone dose after RCI use. When patients who had taken prednisone consistently 24 weeks before the RCI use were analyzed, the mean prednisone dose significantly decreased 1 quarter (12 weeks) after RCI initiation compared to 1 quarter before RCI initiation (15.86 ± 1.71 mg per day to 11.47 ± 1.63 mg per day) in RA but not in SLE or DM/PM (Table 2). More longitudinal data were obtained and the trend of decrease in prednisone continued 1 year (4 Quarters) after RCI initiation (Figure 2).

## Discussion

RCI is thought to exert anti-inflammatory effects by stimulation of endogenous corticosteroid production and possibly through activation of MCRs.[1] Melanocortins are a family of

**Table 2.** Mean Prednisone Dose One Quarter Before and After RCI Initiation.

| | RA | SLE | DM/PM |
|---|---|---|---|
| Number of patients | 201 | 131 | 121 |
| Mean pre-Q1[a] (mg) | 15.86 ± 1.71 | 17.39 ± 2.27 | 17.31 ± 2.18 |
| Mean post-Q1[a] (mg) | 11.47 ± 1.63 | 13.05 ± 2.27 | 12.98 ± 2.34 |

Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; DM, dermatomyositis; PM, polymyositis.
*Confidence intervals are calculated with a 95% confidence level.

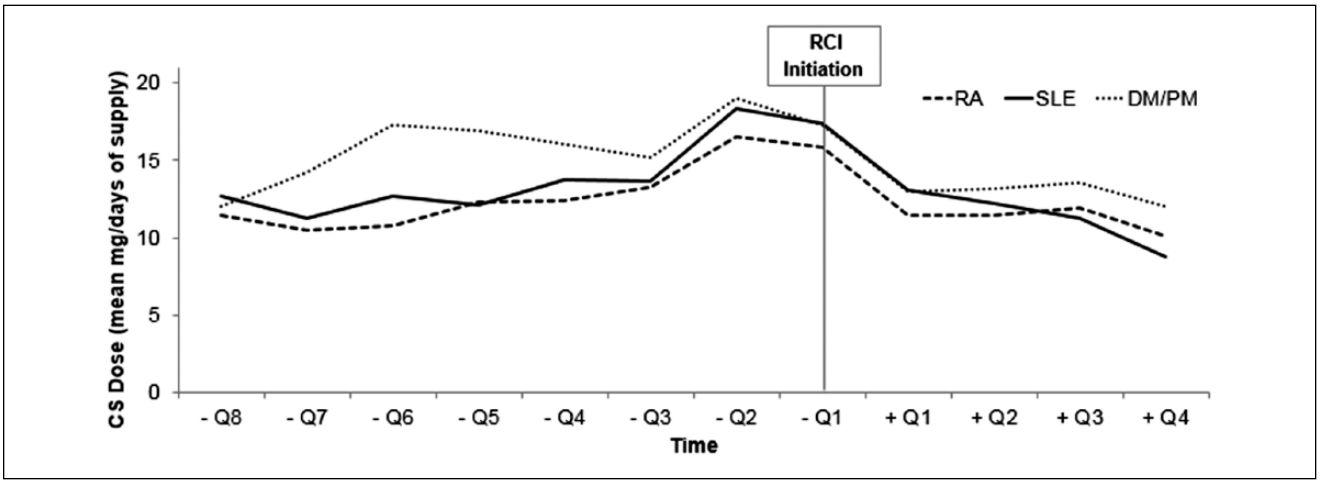


**Figure 2.** Corticosteroid (CS) dose trends in patients who had 24 weeks of consistent use before repository corticotropin.

peptides derived from the common precursor protein pro-opiomelanocortin and they exert biological activity on 5 subtypes of MCRs expressed on immune, skin, muscle bone, kidney, and the central nervous system cells.[5] RCI not only actives MC2R to stimulate steroidogenesis, it also acts on MC3R, which regulates immune cell function, and MC4R, which regulates neuronal interactions and autonomic functions.[6-9] Studies to elucidate the role of melanocortin pathways in autoimmune conditions are still ongoing. As an example, Loram and colleagues suggest that melanocortin peptides may reduce disease activity through regulation of B and T lymphocytes and macrophages.[5]

SLE is caused by inflammation through immune complex deposition in the microvasculature, resulting in vasculitis and occlusive vasculopathy.[10] By binding to MCRs, melanocortin peptides can inhibit canonical pro-inflammatory transcription factor nuclear factor kappa B (NF-κB).[11,12] Studies have shown that inhibition of NF-κB of activated B cells leads to suppression of pro-inflammatory cytokine production including interleukin (IL)-1, IL-6, interferon-γ, tumor necrosis factor-α (TNF-α), IL-2, and IL-17.[13] Melanocortin peptides may also promote immunosuppression by increasing the expansion of regulatory T cells, upregulating anti-inflammatory cytokines such as IL-10.[13] Even though not shown in SLE patients, RCI use in 24 sarcoidosis patients showed more than 10% drop in serum level of SCL 40L, IL-1RA, IL-7, IL-8, MCP-1, MIP-1, MIP-1-β, and TNF-α.[14]

In addition, melanocortin peptides are shown to downregulate various cytokines, co-stimulatory receptors, growth factors, and innate signaling mechanisms.[5] In addition, Loram and colleagues propose that there are direct effects on organs such as endothelial cells to reduce vascular inflammation as well as podocytes, tubular cells, endothelial cells, and mesangial cells for direct kidney protection.[5]

Fiechtner and Montroy carried a single-site open-label trial of RCI in moderately to severely active SLE patients. Ten female patients were treated with RCI for 7 to 15 days and SLEDAI-2K improvement was reached at all observation times (weekly for 28 days) without serious adverse events.[15]

Even though the role of RCI has not been extensively studied in RA, it is thought that melanocortin peptide is produced at the site of inflammation to downregulate inflammation.[14] Catania et al showed that α-melanocyte-stimulating hormone levels are increased in synovial fluid of patients with RA and juvenile chronic arthritis.[13,16] A retrospective case study by Levine showed that 5 out of 5 patients with DM/PM who were started on 80 units of RCI twice weekly had clinical improvement at 12 weeks without significant side effects.[17]

Our study showed that a total of 2749 patients with SLE, RA, and DM/PM from the Symphony claims database were treated with RCI. The majority of patients received 80 units, 2

times a week for an average of 115 to 157 days. When medication use was looked at 6 months after the RCI use, there was a significant decline in NSAID, DMARD, and prednisone use in SLE and RA. For DM/PM, significant decrease was present in DMARD and prednisone. Mean prednisone dose in RA was significantly lower after RCI use but not in SLE and DM/PM.

A strength of our study is the volume of data from a national claims database, which allows some insight to RCI use in a real-world setting. Also, this study provides some exploratory retrospective data to evaluate changes in concurrent medications in patients being treated with RCI.

## Limitations

Our study has several limitations. There are many confounding factors such as comorbidities and disease activities influencing medication changes that were not controlled. In addition, diagnoses and medication use were recorded though ICD-9 codes and outpatient (CMS 1400), institutional (CMS 1500), and pharmacy claims. As a result, no information is available on the certainty of diagnoses or disease activity. DMARDs were combined as one group, and we do not have information on what specific DMARDs were reduced in each rheumatologic condition nor side effects and toxicity. Additionally, we do not have information on clinical consequences such as DAS-28 or SLEDAI scores after RCI administration nor side effects from RCI use. Last, the duration of follow-up is short and our result does not extrapolate to a long-term effect. Further prospective study will be needed to address disease activities during and after RCI use and look at clinical impact of reduction in prednisone use.

## Conclusions

The use of RCI in patients with RA, SLE, or DM/PM may reduce the use of prednisone, DMARDs, and other biologics. This reduction of background medications may indicate better disease control of the autoimmune disorders. For difficult to treat patients, a different approach to manage their complex medication regimens can be helpful for clinicians. In addition, the findings from this research can inform future study design to generate deeper insights for the care of patients with rheumatologic conditions.

### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Winnie W. Nelson is an employee of Mallinckrodt Pharmaceuticals. Gihyun Myung and Maureen A. McMahon have no conflicts of interest to disclose.

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### References

1. Decker DA, Grant C, Oh L, Becker PM, Young D, Jordan S. Immunomodulatory effects of H.P. Acthar Gel on B cell development in the NZB/W F1 mouse model of systemic lupus erythematosus. *Lupus*. 2014;23:802-812.
2. Gettig J, Cummings JP, Matuszewski K. H.P. Acthar gel and cosyntropin review. *P T*. 2009;34:250-257.
3. Schiöth HB, Muceniece R, Larsson M, Wikberg JE. The melanocortin 1, 3, 4 or 5 receptors do not have a binding epitope for ACTH beyond the sequence of alpha-MSH. *J Endocrinol*. 1997;155:73-78.
4. Symphony Health Solutions. Putting healthcare data to work for you. http://symphonyhealth.com/wp-content/uploads/2014/12//IDV-Infographic.pdf.
5. Loram LC, Culp ME, Connolly-Strong ED, Sturgill-Koszycki S. Melanocortin peptides: potential targets in systemic lupus erythematosus. *Inflammation*. 2015;38:260-271.
6. Chan LF, Metherell LA, Clark AJ. Effects of melanocortins on adrenal gland physiology. *Eur J Pharmacol*. 2011;660:171-180.
7. Magenis RE, Smith L, Nadeau JH, Johnson KR, Mountjoy KG, Cone RD. Mapping of the ACTH, MSH, and neural (MC3 and MC4) melanocortin receptors in the mouse and human. *Mamm Genome*. 1994;5:503-508.
8. Mountjoy KG, Mortrud MT, Low MJ, Simerly RB, Cone RD. Localization of the melanocortin-4 receptor (MC4-R) in neuroendocrine and autonomic control circuits in the brain. *Mol Endocrinol*. 1994;8:1298-1308.
9. Lasaga M, Debeljuk L, Durand D, Scimonelli TN, Caruso C. Role of alpha-melanocyte stimulating hormone and melanocortin 4 receptor in brain inflammation. *Peptides*. 2008;29:1825-1835.
10. Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. *J Clin Pathol*. 2003;56:481-490.
11. Manna SK, Aggarwal BB. Alpha-melanocyte-stimulating hormone inhibits the nuclear transcription factor NFkappa B activation induced by various inflammatory agents. *J Immunol*. 1998;161:2873-2880.
12. Mandrika I, Muceniece R, Wikberg JE. Effects of melanocortin peptides on lipopolysaccharide/interferon-gamma-induced NF-kappaB DNA binding and nitric oxide production in macrophage-like RAW 264.7 cells: evidence for dual mechanisms of action. *Biochem Pharmacol*. 2001;61:613-621.
13. Catania A, Gatti S, Colombo G, Lipton JM. Targeting melanocortin receptors as a novel strategy to control inflammation. *Pharmacol Rev*. 2004;56:1-29.
14. Culver D, Abraham S, Lower E, Baughman R. Changes in the cytokine profile of sarcoidosis patients treated with Acthar gel [Abstract]. *Chest*. 2016;150(4 suppl):513A.
15. Fiechtner JJ, Montroy T. Treatment of moderately to severely active systemic lupus erythematosus with adrenocorticotropic hormone: a single-site, open-label trial. *Lupus*. 2014;23:905-912.
16. Catania A, Gerloni V, Procaccia S, et al. The anticytokine neuropeptide α-melanocyte-stimulating hormone in synovial fluid of patients with rheumatic diseases: comparisons with other anticytokine molecules. *Neuroimmunomodulation*. 1994;1:321-328.
17. Levine T. Treating refractory dermatomyositis or polymyositis with adrenocorticotropic hormone (ACTH) gel: a retrospective case series. *Drug Des Devel Ther*. 2012;6:133-139.